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Acute Myelomonocytic Leukemia Following Splenectomy in a Patient With Long-Standing Hodgkin Disease

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THE ASSOCIATION OF acute nonlymphocytic leukemia with Hodgkin disease has been recorded in more than 100 instances.[1-4] In most of these cases the patient has had long-standing Hodgkin disease and radiotherapy has been carried out. The combination of previous radiotherapy and chemotherapy appears to further increase the risk of leukemia developing.

In a patient under our care with Hodgkin disease acute myelomonocytic leukemia developed following splenectomy for hypersplenism. The onset of acute leukemia immediately following splenectomy in a patient with Hodgkin disease has not previously been noted. In addition, because the patient's usual bone marrow sampling sites were hypoplastic, we utilized an ^{111}indium chloride bone marrow scan[5] to find a site that was accessible for aspiration.

Report of a Case

A 26-year-old man presented in June 1967 with cervical lymphadenopathy, night sweats and a 15-pound weight loss over several months. On examination diffuse adenopathy and hepatosplenomegaly were noted. A cervical lymph node biopsy study showed the presence of Hodgkin disease, nodular sclerosing type (Figure 1). Bone marrow aspirate was normal. Initially, nitrogen mustard was administered with incomplete regression (Table 1). Radiotherapy was then given, in addition to administration of chlorambucil and cyclophosphamide; apparent control was achieved. Recurrent adenopathy in 1971 led to the substitution of the MOPP (nitrogen mustard, vincristine, procarbazine, prednisone) regimen with a favorable response. After six cycles, chemotherapy was discontinued, but a lumbar spine lesion necessitated further radiotherapy to L-4. Another course of MOPP was given in 1972 and continued as maintenance every other month for 18 months. In July 1974 increasing splenomegaly and pancytopenia were noted (Table 2). Bone marrow aspirations and needle biopsy studies of each posterior iliac spine showed notably hypocellular marrow. A trial of bleomycin was not beneficial. Because of persistent pancytopenia, felt to be secondary to hypersplenism in part, splenectomy was carried out on October 29, 1974. The spleen weighed 1,100 grams and grossly nodular areas were noted. On microscopic sections there were multinucleated cells consistent with Reed-Sternberg cells (Figure 2).[6] Blood counts improved after splenectomy, but a progressive leukocytosis ensued with increasing numbers of immature forms (Table 2). A sternal bone marrow aspirate was hypocellular with a nondiagnostic pattern. On December 13, 1974, a bone marrow scan was done with ^{111}indium chloride; it showed minimal marrow function in the axial skeleton (Figure 3), but considerable activity about both knee joints

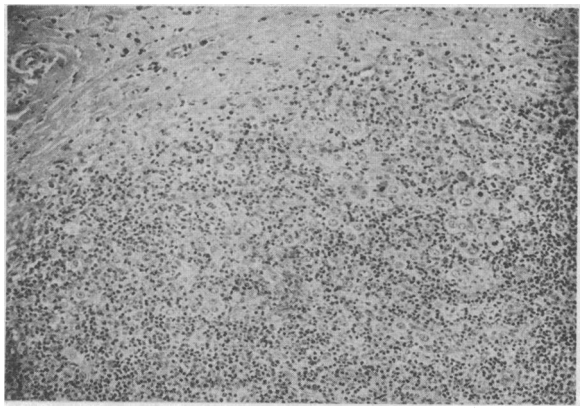

Figure 1.—Original lymph node biopsy specimen showing a pattern of noduler-sclerosing Hodgkin disease. (Reduced from ×120)

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TABLE 1.—*Therapy Administered During Course of Hodgkin Disease*

Dates	*Therapy*
6/67-8/67	Nitrogen mustard
8/67	Irradiation left cervical and left inguinal nodes, 2,500 rads
1/68	2,500 rads to left supraclavicular region
3/68-1/71	Chlorambucil; cyclophosphamide briefly in 1968
1/71-8/71	MOPP—six cycles
12/71	Irradiation of lumbar spine to 2,500 rads
1/72-4/73	MOPP—six cycles followed by maintenance every two months
7/74	Cyclophosphamide and prednisone
8/74	Bleomycin

MOPP = a regimen of nitrogen mustard, vincristine, procarbazine and prednisone

TABLE 2.—*Pertinent Hematological Data During the Patient's Final Year*

Date	*Hematocrit Percent*	*Platelets* $\times 10^3$	*Leukocyte Count* $\times 10^3$	*Blasts Percent*
5/ 1/74	36.5	226	7.6	0
7/ 3/74	26.3	75	2.1	0
10/ 2/74	13.0	45	1.2	0
10/22/75	16.0	40	0.9	0
10/29/74, Splenectomy				
10/31/74	32.4	45	5.1	"Rare"
11/13/74	27.4	130	14.5	8
11/27/74	26.8	230	23.5	19
12/11/74	24.8	350	33.1	43
12/18/74	19.8	259	40.0	47

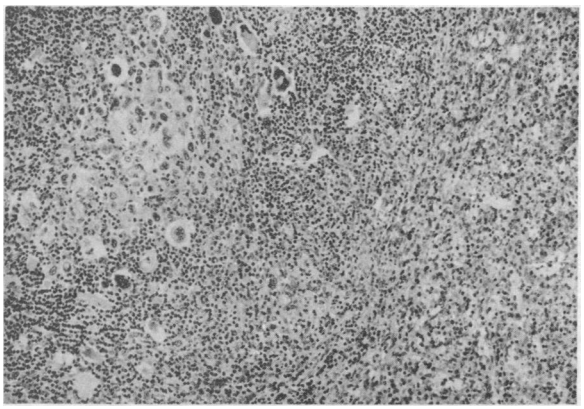

Figure 2.—Spleen, multinucleate cells consistent with Reed-Sternberg cells are seen. (Reduced from ×140)

(Figure 4). Therefore, a bone marrow aspiration from the left proximal tibia was done on December 18, 1974. The peripheral blood smear (Figure 5) showed 47 percent blast forms, many of which had monocytoid features. No Auer rods were seen. The bone marrow smear was hypercellular with numerous myeloblasts consistent with the diagnosis of myelomonocytic leukemia (Figure 6). Cytogenetic studies of this marrow showed a karyotype of 45 XY 2P-/C- (Figure 7).

The patient's subsequent course progressively

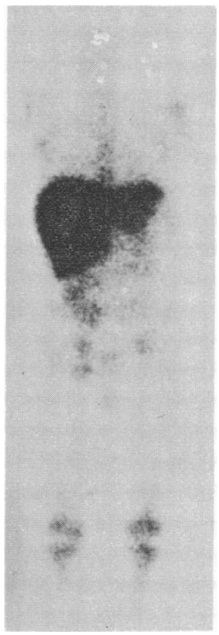

Figure 3.—^{111}Indium chloride total body scan showing diminished activity in the axial skeleton.

deteriorated; there was no evidence of response to therapy with doxorubicin hydrochloride (Adriamycin®), cytosine arabinoside, 6-thioguanine and prednisone. His course was complicated by septicemia, and the patient died on February 10, 1975.

On autopsy, widespread Hodgkin disease and leukemic infiltration of most visceral organs were noted. Review of the spleen slides did not show any leukemic infiltrates.

Discussion

Acute nonlymphocytic leukemia occurring in the course of Hodgkin disease has increasingly been noted in the last few years.[1-4] The most common characteristics of the patients reported include a prolonged period between the diagnosis of Hodgkin disease and the onset of leukemia; the mean duration is usually in excess of five years. Previous irradiation is another important

factor; apparently, its combination with chemotherapy enhances the risk for the development of leukemia. The response to therapy is very poor and the median survival after onset is one to three months. Our patient, therefore, is not exceptional in the duration of disease or previous therapy. The association of ionizing radiation with acute leukemia has been well documented in numerous studies of atomic bomb survivors[7-9] and population groups with significant exposure to diagnostic or industrial radiation.[10-17] On the other hand, Hutchison[18] reviewed a large series of women receiving radiotherapy for cervical cancer and found no increased incidence of leukemia. It is conceivable that Hodgkin disease is a preleukemic state and the longevity of these patients allowed this natural history to become apparent. This theory is interesting; however it is unlikely because in most long-term survivors leukemia never develops. Chemotherapy with melphalan has recently been associated with the development of acute nonlymphocytic leukemia in patients with multiple myeloma[19] and in women with ovarian carcinoma.[20] Another intriguing possibility is that the same biologic aberration leading to Hodgkin disease (that is, viral infection) may also be expressed clinically as acute myeloid leukemia.

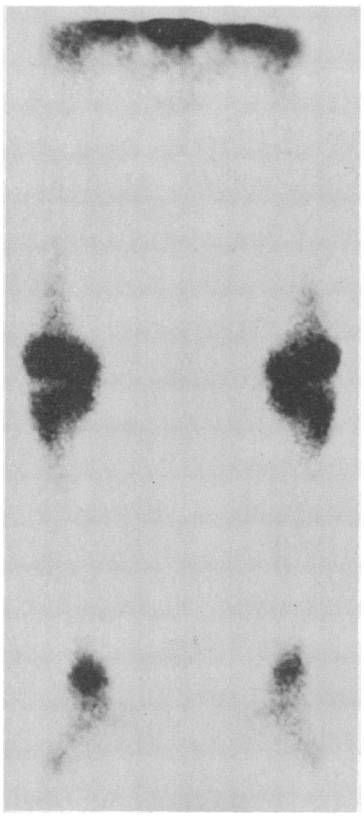

Figure 4.—^{111}Indium chloride scan showing spot views of both knees; increased activity is shown.

Splenectomy for staging in Hodgkin disease has been established as an important component of patient management;[21] however, as a procedure for hypersplenism in this disease its use is not as well known. Rosenthal[22] first suggested in 1948 that splenectomy might be useful in leukopenic states to allow normalization of the granulocyte counts and further chemotherapy. Nies and Creger[23] later showed that patients with lymphoma and cytopenias secondary to hypersplenism respond quite favorably to splenectomy. Subsequent to splenectomy, chemotherapy in effective dosage could be safely resumed. Lowenbraun and co-workers[24] have shown that in cases of Hodgkin disease splenectomy was very useful in the management of their group of patients with cytopenias and hypersplenism. The resumption of chemotherapy at therapeutic dosage led to a high response rate. Although our patient had

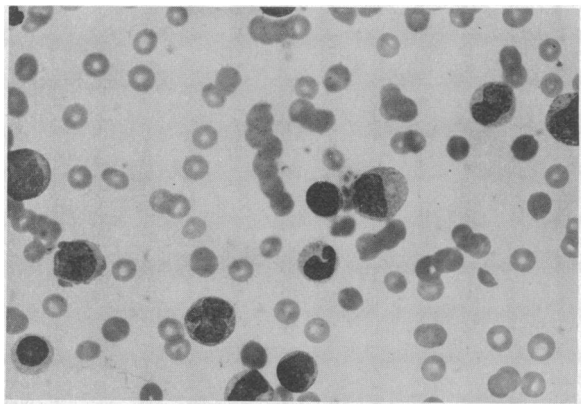

Figure 5.—Peripheral blood smear showing blast forms. (Reduced from ×630)

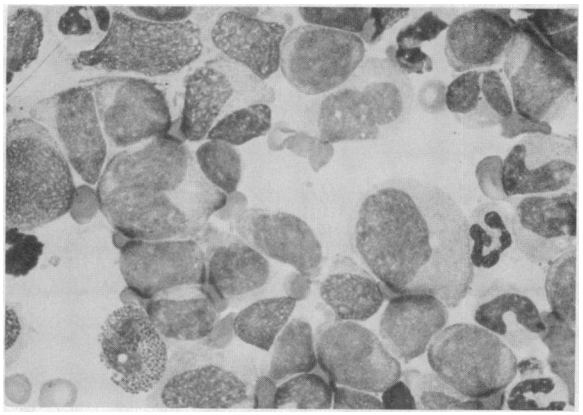

Figure 6.—Bone marrow aspirate showing numerous myeloblasts consistent with acute myelomonocytic leukemia. (Reduced from ×888)

significant marrow hypocellularity, we felt that hypersplenism was playing a significant role in the progressive pancytopenia and, therefore, a splenectomy was carried out. What role the splenectomy had in the appearance of the leukemia is unclear; however, there was no evidence for leukemia before splenectomy and the spleen was free of leukemic infiltration. The onset of overt leukemia in the immediate postoperative period has heretofore not been reported.

Cytogenetic evaluation of the bone marrow aspirate was done and deletion of a C-group chromosome and a portion of the short arms of chromosome 2 was noted. Chromosomal analyses in more than 20 patients in whom acute leukemia developed during the course of Hodgkin disease have been reported.[4,25,26] Abnormalities were universally present; hypodiploidy was frequent. Hodgkin disease, per se, has been shown to be associated with chromosomal aberrations; however, this has not been a consistent finding. We feel that the abnormalities noted in our patient were associated with the leukemic transformation. Chromosomal aberrations in acute myeloid leukemia are well described and the C-group appears to be a common site of abnormality.[27,28]

Finally, our patient presented a diagnostic problem. In the presence of blastic cells in the peripheral blood, neither iliac crest nor sternal marrow aspirations were diagnostic for leukemia. In fact, the iliac crest biopsy specimen was hypoplastic probably because of previous radiotherapy in adjacent areas. We therefore utilized ^{111}indium chloride to detect functioning erythropoietic marrow; a successful bone marrow aspiration specimen was obtained from the proximal tibia confirming the leukemic transformation. We are unaware that this scanning agent has been used successfully in this manner previously. ^{111}Indium chloride is a radionuclide that is very useful for imaging erythropoietic bone marrow.[5] Chemically ionic indium shares many properties with iron. When mixed with serum or injected at acid pH it readily binds to transferrin and therefore appears to compete with iron. Its bone marrow uptake is less complete than iron, resulting in a higher level of tissue background.[29] It is incorporated into erythroid precursors, probably in a similar manner as with iron. The transfer and incorporation allow one to image the functioning marrow with a nuclear medicine scanning device. Theoretically, radioisotopes of iron should be best for marrow imaging, but those available are not suitable for conventional imaging equipment. ^{99m}Technetium sulfur colloid has been used to image the reticuloendothelial component of the marrow, but it is only in the normal state that one can assume that the erythropoietic and reticuloendothelial compartments are identical. Therefore, at present ^{111}indium chloride is the only practical tracer available for erythropoietic imaging in a diseased state.[30] When the marrow is replaced by a myelophthisic process or suppressed by cytotoxic agents, or irradiation, no ^{111}indium

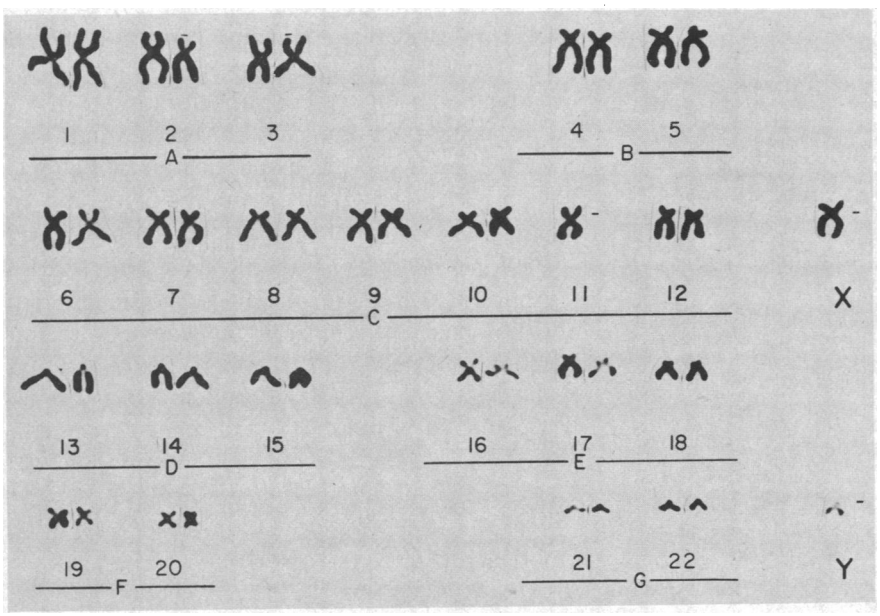

Figure 7.—Cytogenetic study showing a karyotype of 45 XY 2P-/C-. (2P-/C- is the nomenclature to indicate that a portion of the short arms of chromosone 2 and a C group chromosome is missing.)

chloride uptake occurs in the affected areas.[31] Consequently, its use in this case was ideal and the results obtained were gratifying.

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Infective Endocarditis Caused by Moraxella kingae

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THE ROLE OF Moraxella kingae and closely related Gram-negative, pleomorphic bacilli (of the genera Neisseria, Bacteroides, Brucella, Hemophilus, Actinobacillus and Pasteurella) in human disease needs further definition. One previous case of endocarditis caused by Moraxella kingae or new species I has been reported in a 4-year-old child with a ventricular septal defect.[1] The following case documents infective endocarditis due to this organism in an adult.

Report of a Case

A 28-year-old man, a previously healthy lifeguard, had sudden onset of shaking chills, temperatures to 40°C (104°F), myalgias and headaches on June 23, 1976, three days after an abrasion on the right great toe. On June 27, a severe pain in the right femoral region lasted for several hours. On July 1, a half-hour episode of expressive aphasia during temperature elevation to 40°C led to hospital admission. A cardiac murmur was not noted on two previous physical examinations. The patient jogged and swam regularly and in competition without any apparent difficulty. He did not use drugs.

Abnormal findings on physical examination were: a flushed, acutely ill appearance; scleral injection and a hairline abrasion on the dorsum of the right great toe. Blood pressure was 130/80 mm of mercury, pulse 100 and regular, temperature 37°C (98.6°F). A right subconjunctival

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